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14. ABSTRACT
BRCA1 and *BRCA2* (*BRCA1/2*) are key components of the Fanconi anemia (FA)/homologous recombination (HR) pathway of DNA repair. Cancer cells with deleterious FA/HR pathway mutations are hypersensitive to poly(ADP-ribose) polymerase (PARP) inhibitors. However, only about half of the cancer patients with germline FA/HR pathway mutations respond to PARP inhibitors, raising the question of why a substantial fraction of HR-deficient cancers are resistant to these agents in the clinic. Based on previous work in the Swisher and Kaufmann laboratories, we proposed to test the **hypothesis** that *two different conditions must be met for ovarian cancer to be hypersensitive to platinum and PARP inhibitors: The FA/HR pathway must remain disabled and NHEJ must remain intact and functional.* Our aim is to **Correlate biomarkers of HR deficiency and NHEJ pathway integrity in pre-treatment biopsies with response to a PARPi in a prospective single-agent PARPi phase 2 clinical trial in recurrent ovarian carcinoma.** Over the past 12 months we have i) completed IRB and HRPO review of our project, ii) developed sequencing and genomic scarring assay to assess large number of DNA repair genes on small core biopsy specimens iv) begun accessioning samples from the phase 2 rucaparib trial (Ariel 2, NCT01891344).

15. SUBJECT TERMS
ovarian cancer, drug resistance, rucaparib, phase 2, DNA repair, homologous recombination, nonhomologous end-joining (NHEJ), poly(ADP-ribose) polymerase, BRCA1, BRCA2, PARP1

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INTRODUCTION

Poly(ADP-ribose) polymerase (PARP) is an abundant nuclear enzyme that regulates five different DNA repair pathways (1, 2). Building on preclinical observations that defects in homologous recombination (HR) repair, which are found in 30-50% of ovarian cancers, sensitize cells to killing by PARP inhibitors (3-5), five separate phase 3 trials involving PARP inhibitors have opened or are about to open in ovarian cancer (2). Nonetheless, in a recent decision the Food and Drug Administration has declined to approve the PARP inhibitor olaparib for ovarian cancer, citing (in part) the need for additional information that will permit better identification of patients most likely to respond to this agent. In collaboration with Scott Kaufmann (Mayo Clinic), the present synergistic translational leverage project is assessing multiple aspects of DNA repair pathway integrity in pretreatment biopsies from a large multi-institution phase 2 study of the PARP inhibitor rucaparib. In particular, the Swisher laboratory is using massively parallel DNA sequencing to assess mutations in the HR pathway, the nonhomologous end-joining (NHEJ) pathway, PARP1 and other DNA repair genes that could impact response to PARP inhibitors.

Key words: ovarian cancer, drug resistance, rucaparib, phase 2, DNA repair, homologous recombination, nonhomologous end-joining (NHEJ), poly(ADP-ribose) polymerase, BRCA1, BRCA2, PARP1,

Overall Project Summary:

Consistent with our Statement of Work, we prepared paperwork for the IRB and HRPO regarding the analysis of deidentified samples from the phase 2 rucaparib trial. Both determined that the research was exempt.

Sample acquisition: The phase 2 clinical trial that is providing samples for the correlative assays in the Kaufmann and Swisher laboratories (ClinicalTrials.gov identifier NCT01891344) opened during the reporting period. Deidentified specimens from 30 patients were obtained through November 15, 2014, and are being stored for evaluation in batches.

Preparation for evaluation of the clinical trial specimens:
The needle biopsy specimens obtained prior to treatment initiation on ARIEL2 are tiny, necessitating alterations in our established protocol for BROCA sequencing. We have spent significant time testing various modifications to the protocol to optimize:

1. DNA yield and integrity from the small formalin- fixed paraffin embedded (FFPE) specimens.
2. Library preparation to allow sequencing of 50 ng of DNA
3. Bioinformatics pipeline

At the present, we are still working on a few more modification for library preparation. It is critical that all steps are optimized to ensure that we obtain optimal data from the precious and limited clinical specimens.

Key research accomplishments

Nothing to report (per instructions that hitting project milestones are not key research accomplishments)

Conclusions

We have made progress in optimizing protocols for analysis of the clinical trial specimens and are actively acquisitioning the clinical trial specimens. Thus, we are on track to acquisition and sequence all samples before the end of the funding period in two years.

Publications, abstracts and presentations

1. Swisher EM, McNeish IA, Coleman RL, Brenton J, Kaufmann SH, Allen AR, Raponi M, Giordano H, Maloney L, Isaacson J, Ledermann JA. ARIEL 2/3: An integrated clinical trial program to assess activity of rucaparib in ovarian cancer and to identify tumor molecular characteristics predictive of response. Journal of Clinical Oncology 2014;32:5S:suppl; abst TPS5619.

Inventions, patents and licenses

None

Reportable Outcomes

None

Other achievements

None

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5. Ashworth A. A Synthetic Lethal Therapeutic Approach: Poly(ADP) Ribose Polymerase Inhibitors for the Treatment of Cancers Deficient in DNA Double-Strand Break Repair. J Clin Oncol 2008;26:3785-90.

Appendices

None